UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/288,344	04/08/99	SEIDMAN E	P-PM-3474

HM12/0425

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EXAMINER	
CRANE, L	
ART UNIT	**PAPER NUMBER**
1623	9

DATE MAILED: 04/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/288,344	Seidman et al.	
Examiner	Group Art Unit	
L. E. Crane	1623	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ----3---- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 8/30/99 (IDS) and 02/07/00 (Amdt A & IDS)-----

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-46 ---------- is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-46 ---------- is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 & 8--

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

No claims have been cancelled and new claims **35-46** have been added as per the preliminary amendments filed February 7, 2000. Information Disclosure Statements and references filed August 30, 1999 and February 7, 2000 have been received, considered and entered.

Claims **1-46** remain in the case.

Claims **1, 7, 19, 30, 35 and 46** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim **1**, line 2, the term "6-mercaptopurine drug treatment" contains a superfluous term ("drug") which may be deleted without changing the meaning of the term or the claim. This same problem reoccurs in claims **7, 19, 30, 35 and 46**.

Applicant's arguments filed February 7, 2000 have been fully considered but they are not persuasive.

Applicant argues at page 7 et seq of the instant response to the effect that the noted terms are proper because they refer to compounds "such as 6-mercaptopurine and azathioprine." Examiner notes that this explanation is interesting because it shows how applicant has used the noted terms as a Trojan Horse, i.e. to permit

the effective insertion of the term "such as" without actually inserting the term. But, since applicant has made the clear assertion that a "such as" term is equivalent to the noted terms, examiner maintains the instant rejection noting that the "such as" like terms cited above are also per se indefinite.

In claim **1**, line 4, the term "a 6-mercaptopurine drug" contains a superfluous terms ("a" and "drug") which may be deleted without changing the meaning of the term or the claim. This same problem reoccurs in claims **7, 19, 30 and 35**.

Applicant's arguments filed February 7, 2000 have been fully considered but they are not persuasive.

This is another "such as" example. Applicant is requested to delete the noted term because said term is both superfluous and also effectively per se indefinite, to insert the names of all active ingredients intended, or other appropriate action.

In claim **1**, line 13, the term "6-mercaptopurine drug" contains a superfluous term ("drug") which may be deleted without changing the meaning of the term or the claim. This same problem reoccurs in claims **7, 19** (all four occurrences) **and 30**, and in claim **7**, line 2; claim **13**, line 2; and claim **29**, line 2. See also claims **35 & 46.**

Applicant's arguments filed February 7, 2000 have been fully considered but they are not persuasive.

Applicant is referred to the first two responses to applicant's arguments above.

The following is a quotation of 35 U.S.C. §103(**a**) which forms the basis for all obviousness rejections set forth in this Office action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

Claims **1-46** are rejected under 35 U.S.C. §103(a) as being unpatentable over Sandborn (PTO-892 ref. **R**) in view of Sandborn **'915** and further in view of Berkow et al. (PTO-892 ref. T).

The instant claims are directed to the administration of 6-mercaptpurine, 6-thioguanine or azathioprine to treat an immune-related gastrointestinal disorder, e.g. Crohn's disease, colitis, inflammatory bowel disease (IBD), or a related disorder, as well as high performance liquid chromatography (HPLC) test protocols for patient monitoring to insure minimization of undesirable side effects.

The Sandborn reference is a review article which describes the medicinal activity of azathioprine(AZA)/6-mercaptopurine (6-MP) in the treatment of Crohn's Disease, inflammatory bowel disease (IBD), ulcerative colitis and related conditions. At column 1 at page 93 this reference makes reference to a Mayo clinic study which determined that genetic factors make some hosts particularly sensitive to blood levels of the noted active ingredients in view of a low level of requisite enzymatic activity required to produce the active metabolite(s) in vivo. At p. 95 this reference discloses toxic effects of AZA/6-MP administration at the second full paragraph of column 1

noting pancreatitis, allergic reactions and drug hepatitis among others. Leukopenia is noted in the third full paragraph.

Sandborn **'915** is directed to the treatment of Crohn's Disease by administration of azathioprine and 6-mercaptopurine and further specifies ranges for blood cell concentrations of 6-thioguanine and 6-methylmercaptopurine, which concentration are taught to be determinable in the disclosure at column 9, line 1 to column 10, line 11. See in particular column 9, lines 53-55 et seq and column 10, lines 4-6 et seq.

Berkow et al. discloses at pages 833-834 under the heading "Immunosuppressive drugs" that azathioprine and 6-mercaptopurine are effective in the treatment of Crohn's Disease, but indicates that side effects including pancreatitis and leukopenia (drug-induced blood cell depletion) are indicia of excessive immunosuppressive drug concentrations and must be avoided.

Disclosure in the prior art of the administration of AZA and/or 6-MP to treat Crohn's Disease and/or IBD and related disease conditions (Sandborn, Sandborn '915 and Berkow) when combined with specific teachings in Sandborn '915 of how to use high performance liquid chromatography (HPLC) to determine drug levels, including drug levels in blood cells, and teachings of side effects to be avoided and the reasons for their occurrence in Sandborn, provides the ordinary practitioner with all of the elements of the instant disclosed invention and appears to leave no definable subject matter which has patentable distinction in view of the noted art. The election of generic testing protocols within the instant claims are deemed to be nothing more than a description of how the information

of the prior art would guide the careful practitioner in the administration of AZA/6-MP to a Crohn's Disease patient, and possibly in particular to a Crohn's Disease patient suffering from genetic limitations which limit the rate of sub-toxic AZA/6-MP administration. For these reasons, no claim has been found to contain patentable subject matter.

Therefore, the instant claimed improvement in the treatment of immune-mediated gastrointestinal disorders including IBD/Crohn's Disease by the monitoring of the administration of 6-mercaptopurine or its prodrug azathioprine (chemical structure provided in PTO-892 ref. S) in order to avoid toxic effects on the blood or the liver of the host being treated would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Applicant's arguments filed February 7, 2000 have been fully considered but they are not persuasive.

Applicant argues that the cited references do "... not teach or suggest the claimed methods of optimizing therapeutic efficacy and/or reducing toxicity associated with 6-MP drug treatment." Examiner respectfully disagrees. As noted in the descriptions of the prior art contents provided above, and within the references themselves in substantially greater detail, the prior art provides all of the requisite guidance to permit the ordinary practitioner to both optimize therapeutic efficacy and minimize associated toxicities while treating a host in need thereof for the disease conditions specified by the instant claims. The remainder of applicant's arguments appear to be directed to the details of specific treatments and the associated

dosage effects on specific host parameters, e.g. blood cell count. Examiner considers these details to be merely another approach to describing the same variables already pointed out in the prior art of record. In view of the fairly detailed guidance provided by the noted prior art the ordinary practitioner has substantial latitude to treat individual hosts in need, to optimize the treatment of the noted disease conditions, and to minimize the undesired side effects using the monitoring technology and associated guidance taught by the prior art. The latitude granted to the ordinary practitioner in practicing and routinely experimenting within the subject matter area disclosed in the noted prior art is deemed to include the subject matter claimed herein. Therefore, applicant's claims and associated arguments must fail as a basis for a finding of patentable distinction. For these reasons the instant rejection has been maintained.

The disclosure is objected to because of the following informalities:

At page 1, lines 5-6, the term " , which is herein incorporated by reference" is improper because only allowed US patent applications and US patents may be incorported by reference. Deletion of this term and deletions of all other similarly improper uses of this term within the disclosure is/are respectfully requested.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE

DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. §1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592** .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639** . The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Gary Geist, can be reached at (703)-308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235** .

LECrane:lec

5 **04/20/00**

PAUL J. KILLOS
PRIMARY EXAMINER
1623